. -318-

We Claim:

5

10

15

20

1. A method of preventing or treating hot flashes, vasomotor symptoms, impulse control disorders, or personality change due to a general medical condition, comprising administering to a patient in need thereof a therapeutically effective amount of a selective norepinephrine reuptake inhibitor selected from the group consisting of:

atomoxetine or a pharmaceutically acceptable salt thereof; racemic reboxetine or a pharmaceutically acceptable salt thereof; (S,S) reboxetine or a pharmaceutically acceptable salt thereof; a compound of formula (I):

wherein X is C_1 - C_4 alkylthio, and Y is C_1 - C_2 alkyl, or a pharmaceutically acceptable salt thereof;

a compound of formula (IA):

wherein n is 1, 2 or 3; R1 is C₂-C₁₀alkyl, C₂-C₁₀alkenyl, C₃-C₈cycloalkyl or C₄-C₁₀cycloalkylalkyl, wherein one C-C bond within any cycloalkyl moiety is optionally substituted by an O-C, S-C or C=C bond and wherein each group is optionally substituted with from 1 to 7 halogen substituents and/or with from 1 to 3 substituents each independently selected from hydroxy, cyano, C₁-C₄alkyl, C₁-C₄alkylthio (optionally substituted with from 1 to 3 halogen atoms) and C₁-C₄alkoxy (optionally substituted

WO 2005/060949

5

10

15

20

25

with from 1 to 3 halogen atoms); R2 is H, C1-C4alkyl (optionally substituted with from 1 to 7 halogen atoms), C_1 - C_4 alkyl- $S(O)_X$ - wherein x is 0, 1 or 2 (optionally substituted with from 1 to 7 halogen atoms), C₁-C₄alkoxy (optionally substituted with from 1 to 7 halogen atoms), cyano, halogen, phenyl (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C1-C4alkyl and C1-C4alkoxy), phenoxy (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C_1 - C_4 alkyl and C_1 - C_4 alkoxy) or - CO_2 (C_1 - C_4 alkyl), or together with R3 forms a further benzene ring (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C1-C4alkyl and C1-C4alkoxy); R3 is H, C1-C₄alkyl (optionally substituted with from 1 to 7 halogen atoms), C₁-C₄alkyl-S(O)_xwherein x is 0, 1 or 2 (optionally substituted with from 1 to 7 halogen atoms), C₁-C4alkoxy (optionally substituted with from 1 to 7 halogen atoms), cyano, halogen, phenyl (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C_1 - C_4 alkyl and C_1 - C_4 alkoxy), phenoxy (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C_1 - C_4 alkyl and C_1 -C4alkoxy) or -CO2(C1-C4alkyl), or together with R2 or R4 forms a further benzene ring (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C₁-C₄alkyl and C₁-C₄alkoxy); R4 is H, C₁-C₄alkyl (optionally substituted with from 1 to 7 halogen atoms), C_1 - C_4 alkyl- $S(O)_{X^-}$ wherein x is 0, 1 or 2 (optionally substituted with from 1 to 7 halogen atoms), C1-C4alkoxy (optionally substituted with from 1 to 7 halogen atoms), cyano, halogen, phenyl (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C₁-C₄alkyl and C₁-C₄alkoxy), phenoxy (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C1-C4alkyl and C1-C4alkoxy) or -CO2(C1-C4alkyl), or together with R3 forms a further benzene ring (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C1-C4alkyl and C1-C4alkoxy); R5 is H, C1-C4alkyl (optionally substituted with from 1 to 7 halogen atoms), C1-C4alkoxy (optionally substituted with from 1 to 7 halogen atoms) or halogen; R6 is H, C1-C4alkyl (optionally substituted with from 1 to 7 halogen atoms), C1-C4alkoxy (optionally

-320-

substituted with from 1 to 7 halogen atoms) or halogen; R7 is H or C_1 - C_4 alkyl; R8 is H or C_1 - C_4 alkyl; R9 is H, halogen, hydroxy, cyano, C_1 - C_4 alkyl or C_1 - C_4 alkoxy; and R10 is H, halogen, hydroxy, cyano, C_1 - C_4 alkyl or C_1 - C_4 alkoxy; or a pharmaceutically acceptable salt thereof, with the proviso that the compound N-ethyl-N-benzyl-4-piperidinamine is excluded;

a compound of formula (IB):

5

10

15

20

wherein Rx is H; Ry is H or C_1 - C_4 alkyl; each Rz is independently H or C_1 - C_4 alkyl; X represents O; Y represents OH or OR; R is C_1 - C_4 alkyl; Ar₁ is a phenyl ring or a 5- or 6-membered heteroaryl ring each of which may be substituted with 1, 2, 3, 4 or 5 substituents (depending upon the number of available substitution positions) each independently selected from C_1 - C_4 alkyl, $O(C_1$ - C_4 alkyl), $S(C_1$ - C_4 alkyl), halo, hydroxy, pyridyl, thiophenyl and phenyl optionally substituted with 1, 2, 3, 4 or 5 substituents each independently selected from halo, C_1 - C_4 alkyl, or $O(C_1$ - C_4 alkyl); and Ar₂ is a phenyl ring or a 5- or 6-membered heteroaryl ring each of which may be substituted with 1, 2, 3, 4 or 5 substituents (depending upon the number of available substitution positions) each independently selected from C_1 - C_4 alkyl, $O(C_1$ - C_4 alkyl) and halo; wherein each above-mentioned C_1 - C_4 alkyl group is optionally substituted with one or more halo atoms; or a pharmaceutically acceptable salt thereof;

a compound of formula (IC)

$$\begin{array}{c|c}
R^1 & A^{R'} \\
R^1 & A^{R'} \\
R^1 & R^{R'} \\
R^1 & R^1
\end{array}$$
(IC)

wherein: A is S or O; R is H; Ar is a phenyl group optionally substituted with 1, 2, 3, 4 or 5 substituents each independently selected from C_1 - C_4 alkyl, $O(C_1$ - C_4 alkyl), $S(C_1$ - C_4 alkyl), halo, hydroxy, $CO_2(C_1$ - C_4 alkyl), pyridyl, thiophenyl and phenyl optionally substituted with 1, 2, 3, 4 or 5 substituents each independently selected from halo, C_1 - C_4 alkyl, or $O(C_1$ - C_4 alkyl); X is a phenyl group optionally substituted with 1, 2, 3, 4 or 5 substituents each independently selected from halo, C_1 - C_4 alkyl, or $O(C_1$ - C_4 alkyl); a C_1 - C_4 alkyl group; a C_3 - C_6 cycloalkyl group or a C_1 - C_4 alkyl; each C_1 is independently H or C_1 - C_4 alkyl; wherein each above-mentioned C_1 - C_4 alkyl group is optionally substituted with one or more halo atoms; or a pharmaceutically acceptable salt thereof; with the proviso that, when A is O, X is a C_1 - C_4 alkyl group, a C_3 - C_6 cycloalkyl group or a C_1 - C_4 cycloalkyl group;

a compound of formula (ID)

5

10

15

$$R^3$$
 $(CH_2)_n$
 N
 CH_3
 H
 Ar

(ID)

wherein -X- is -C(R^4R^5)-, -O- or -S-; n is 2 or 3; R^1 is H or C_1 - C_4 alkyl; R^3 is H, halo, C_1 - C_4 alkyl, O(C_1 - C_4 alkyl), nitrile, phenyl or substituted phenyl; R^4 and R^5 are each independently selected from H or C_1 - C_4 alkyl; Ar- is selected from the group consisting of

(i)
$$R^{2a}$$
 and (ii) R^{2e} R^{2d}

in which R^{2a} is H, halo, methyl or ethyl; R^{2b} is H, halo or methyl; R^{2c} is H, halo, methyl, trifluoromethyl, nitrile, or methoxy; R^{2d} is H, halo, methyl or ethyl; R^{2e} is H, halo, methyl, trifluoromethyl, nitrile, or methoxy; R^{2f} is H, or fluoro; -Y- is -O-, -S- or -N(R^6)-; and R^6 is H or methyl or a pharmaceutically acceptable salt thereof;

a compound of formula (IE)

5

10

15

20

$$\begin{array}{c|c}
R^2 & R^1 \\
\hline
N & 1 \\
N & R^3 & R^4
\end{array}$$
(IE)

wherein R^1 is C_1 - C_6 alkyl (optionally substituted with 1, 2 or 3 halo substituents and/or with 1 substituent selected from -S-(C_1 - C_3 alkyl), -O-(C_1 - C_3 alkyl) (optionally substituted with 1, 2 or 3 F atoms), -O-(C_3 - C_6 cycloalkyl), -SO₂-(C_1 - C_3 alkyl), -CN, -COO-(C_1 - C_2 alkyl) and -OH); C_2 - C_6 alkenyl; -(CH_2)_q- Ar_2 ; or a group of formula (i) or (ii)

$$(CH_2)_r$$
 Z $(CR^5R^6)_s$ $(CH_2)_r$ (CR^5R^6) $(CH_2)_p$ $(CR^7R^8)_t$ $(CR^7R^$

 R^2 , R^3 and R^4 are each independently selected from hydrogen or C_1 - C_2 alkyl; R^5 , R^6 , R^7 and R^8 are at each occurrence independently selected from hydrogen or C_1 - C_2 alkyl; -X- is a bond, -CH₂-, -CH=CH-, -O-, -S-, or -SO₂-; -Y- is a bond, -CH₂- or -O-; -Z is hydrogen, -OH or -O-(C_1 - C_3 alkyl); p is 0, 1 or 2; q is 0, 1 or 2; r is 0 or 1; s is 0, 1, 2 or 3; t is 0, 1, 2 or 3; Ar₁ is phenyl, pyridyl, thiazolyl, benzothiophenyl or naphthyl; wherein said phenyl, pyridyl or thiazolyl group may be substituted with 1, 2 or 3 substituents each independently selected from halo, cyano, C_1 - C_4 alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C_1 - C_4 alkyl) (optionally substituted with 1, 2 or 3 F atoms) and -S-(C_1 - C_4 alkyl) (optionally

substituted with 1, 2 or 3 F atoms) and/or with 1 substituent selected from pyridyl, pyrazole, phenyl (optionally substituted with 1, 2 or 3 halo substituents) and phenoxy (optionally substituted with 1, 2 or 3 halo substituents); and wherein said benzothiophenyl or naphthyl group may be optionally substituted with 1, 2 or 3 substituents each independently selected from halo, cyano, C₁-C₄ alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C₁-C₄ alkyl) (optionally substituted with 1, 2 or 3 F atoms), and -S-(C₁-C₄ alkyl) (optionally substituted with 1, 2 or 3 F atoms); Ar₂ is naphthyl, pyridyl, thiazolyl, furyl, thiophenyl, benzothiophenyl, or phenyl, wherein said naphthyl, pyridyl, thiazolyl, furyl, thiophenyl, benzothiophenyl, or phenyl may be substituted with 1, 2 or 3 substituents each independently selected from halo, C1-C4 alkyl (optionally substituted with 1, 2 or 3 F atoms) and -O-(C1-C4 alkyl) (optionally substituted with 1, 2 or 3 F atoms); or a pharmaceutically acceptable salt thereof; provided that (a) the cyclic portion of the group of formula (i) must contain at least three carbon atoms and not more than seven ring atoms; (b) when -X- is -CH=CH-, then the cyclic portion of the group of formula (i) must contain at least five carbon atoms; and (c) when -Z is -OH or -O-(C₁-C₃ alkyl), then -X- is -CH₂-; (d) when -Y- is -O- then p cannot be 0; and (e) the compound 3-[(phenylmethyl)-(3S)-3-pyrrolidinylamino]-propanenitrile is excluded;

a compound of formula (IF)

$$\begin{array}{c|c}
R^2 & R^1 \\
N & Ar_1 \\
R^3 & R^4
\end{array}$$
(IF)

wherein

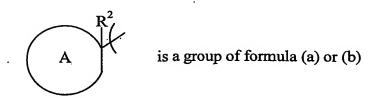
5

10

15

20

-324-



or
$$\mathbb{R}^2$$
 \mathbb{R}^2 \mathbb{R}^2

 R^1 is C_1 - C_6 alkyl (optionally substituted with 1, 2 or 3 halo substituents and/or with 1 substituent selected from -S-(C_1 - C_3 alkyl), -O-(C_1 - C_3 alkyl) (optionally substituted with 1, 2 or 3 F atoms), -O-(C_3 - C_6 cycloalkyl), -SO₂-(C_1 - C_3 alkyl), -CN, -COO-(C_1 - C_2 alkyl) and -OH); C_2 - C_6 alkenyl; -(C_1 - C_2 - C_3 - C_4 - C_5 - C_6 alkenyl; -(C_1 - C_2 - C_6 - C_5 - C_6 - C_6 - C_6 - C_7 - C_8 - C_6 - C_8 -C

5

10

15

20

$$(CH_2)_r$$
 Z $(CR^5R^6)_s$ $(CH_2)_r$ (CR^5R^6) $(CH_2)_p$ $(CR^7R^8)_r$ $(CR^7R^$

 R^2 , R^3 and R^4 are each independently selected from hydrogen or C_1 - C_2 alkyl; R^5 , R^6 , R^7 and R^8 are at each occurrence independently selected from hydrogen or C_1 - C_2 alkyl; -X- is a bond, -CH₂-, -CH=CH-, -O-, -S-, or -SO₂-; -Y- is a bond, -CH₂- or -O-; -Z is hydrogen, -OH or -O-(C_1 - C_3 alkyl); p is 0, 1 or 2; q is 0, 1 or 2; r is 0 or 1; s is 0, 1, 2 or 3; t is 0, 1, 2 or 3; Ar₁ is phenyl, pyridyl, thiazolyl, benzothiophenyl or naphthyl; wherein said phenyl, pyridyl or thiazolyl group may be substituted with 1, 2 or 3 substituents each independently selected from halo, cyano, C_1 - C_4 alkyl (optionally substituted with 1, 2 or 3 F atoms) and -S-(C_1 - C_4 alkyl) (optionally substituted with 1, 2 or 3 F atoms) and -S-(C_1 - C_4 alkyl) (optionally substituted with 1, 2 or 3 halo substituents), benzyl and phenoxy (optionally substituted with 1, 2 or 3 halo substituents); and wherein said benzothiophenyl or naphthyl group may be optionally substituted with 1, 2 or 3 substituents each independently selected from halo, cyano, C_1 - C_4 alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C_1 - C_4 alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C_1 - C_4 alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C_1 - C_4 alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C_1 - C_4 alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C_1 - C_4 alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C_1 - C_4 alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C_1 - C_4 alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C_1 - C_4 alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C_1 - C_4 alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C_1 - C_4 alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C_1 - C_4 alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C_1 - C_4 alkyl (optionally substituted with 1, 2 or 3 F atoms)

C₄ alkyl) (optionally substituted with 1, 2 or 3 F atoms), and -S-(C₁-C₄ alkyl) (optionally substituted with 1, 2 or 3 F atoms); Ar₂ is naphthyl, pyridyl, thiazolyl, furyl, thiophenyl, benzothiophenyl, or phenyl, wherein said naphthyl, pyridyl, thiazolyl, furyl, thiophenyl, benzothiophenyl, or phenyl may be substituted with 1, 2 or 3 substituents each independently selected from halo, C₁-C₄ alkyl (optionally substituted with 1, 2 or 3 F atoms) and -O-(C₁-C₄ alkyl) (optionally substituted with 1, 2 or 3 F atoms); or a pharmaceutically acceptable salt thereof; provided that (a) the cyclic portion of the group of formula (i) must contain at least three carbon atoms and not more than seven ring atoms; (b) when -X- is -CH=CH-, then the cyclic portion of the group of formula (i) must contain at least five carbon atoms; and (c) when -Z is -OH or -O-(C₁-C₃ alkyl), then -X- is -CH₂-; and (d) when -Y- is -O- then p cannot be 0;

a compound of formula (IG)

5

10

15

20

wherein -X- is -S- or -O-; each R is independently selected from H or C_1 - C_4 alkyl; R^1 is H, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, halo, cyano, trifluoromethyl, trifluoromethoxy, -NR³R⁴, -CONR³R⁴, -COOR³ or a group of the formula (i)

$$-z$$
 R^5 ;

 R^2 is C_1 - C_4 alkyl, phenyl or phenyl substituted with 1, 2 or 3 substituents each independently selected from C_1 - C_4 alkyl, C_1 - C_4 alkoxy, nitro, hydroxy, cyano, halo, trifluoromethyl, trifluoromethoxy, benzyl, benzyloxy, -NR⁶R⁷, -CONR⁶R⁷, COOR⁶, -SO₂NR⁶R⁷ and -SO₂R⁶; R⁵ is selected from C_1 - C_4 alkyl, C_1 - C_4 alkoxy, carboxy, nitro, hydroxy, cyano, halo, trifluoromethyl, trifluoromethoxy, benzyl, benzyloxy, -NR⁸R⁹, -CONR⁸R⁹, -SO₂NR⁸R⁹ and -

-326-

SO₂R⁸; R³, R⁴, R⁶, R⁷, R⁸ and R⁹ are each independently selected from H or C₁- C₄ alkyl; and -Z- is a bond, -CH₂-, or -O-; or a pharmaceutically acceptable salt thereof and a compound of formula (IH)

5

15

20

25

wherein,

X is OH, C1-C4 alkoxy, NH2 or NH(C1-C4 alkyl);

Rx is H or C1-C4 alkyl;

Ry is H or C1-C4 alkyl;

each Rz group is independently H or C1-C4 alkyl, with the proviso that not more than 3 Rz groups may be C1-C4 alkyl;

R1 is C1-C6 alkyl (optionally substituted with 1, 2 or 3 halogen atoms and/or with 1 substituent selected from C1-C4 alkylthio (optionally substituted with 1, 2 or 3 fluorine atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 fluorine atoms), C3-C6 cycloalkoxy, C1-C4 alkylsulfonyl, cyano, -CO-O(C1-C2 alkyl), -O-CO-(C1-C2 alkyl) and hydroxy); C2-C6 alkenyl (optionally substituted with 1, 2 or 3 halogen atoms); C3-C6 cycloalkyl (optionally substituted with 1, 2 or 3 halogen atoms and/or with 1 substituent selected from C1-C4 alkoxy and hydroxy) wherein one C-C bond within the cycloalkyl moiety is optionally substituted by an O-C, S-C or C=C bond; C4-C7 cycloalkylalkyl (optionally substituted with 1, 2 or 3 halogen atoms and/or with 1 substituent selected from C1-C4 alkoxy and hydroxy) wherein one C-C bond within the cycloalkyl moiety is optionally substituted by an O-C, S-C or C=C bond; or CH2Ar2; and Ar1 and Ar2 are each independently a phenyl ring or a 5- or 6-membered heteroaryl ring each of which is optionally substituted with 1, 2 or 3 substituents (depending upon the number of available substitution positions) each independently selected from C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkylthio (optionally substituted with 1, 2 or 3 halogen atoms), -CO-O(C1-C4 alkyl), cyano, -NRR, -CONRR, halo and hydroxy

5

10

15

20

and/or with 1 substituent selected from pyridyl, thiophenyl, phenyl, benzyl and phenoxy each of which is optionally ring-substituted with 1, 2 or 3 substituents each independently selected from halogen, C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), carboxy, nitro, hydroxy, cyano, -NRR, -CONRR, SO₂NRR and SO₂R); and each R is independently H or C1-C4 alkyl;

or a pharmaceutically acceptable salt thereof.

2. Use of a selective norepinephrine reuptake inhibitor for the manufacture of a medicament for the treatment of hot flashes, vasomotor symptoms, impulse control disorders, or personality change due to a general medical condition,

wherein said selective norepinephrine reuptake inhibitor is selected from the group consisting of:

atomoxetine or a pharmaceutically acceptable salt thereof; racemic reboxetine or a pharmaceutically acceptable salt thereof; (S,S) reboxetine or a pharmaceutically acceptable salt thereof; a compound of formula (I):

wherein X is C_1 - C_4 alkylthio, and Y is C_1 - C_2 alkyl, or a pharmaceutically acceptable salt thereof;

a compound of formula (IA):

-328-

HN

5

10

15

20

25

(AI)

wherein n is 1, 2 or 3; R1 is C2-C10alkyl, C2-C10alkenyl, C3-C8cycloalkyl or C4-C₁₀cycloalkylalkyl, wherein one C-C bond within any cycloalkyl moiety is optionally substituted by an O-C, S-C or C=C bond and wherein each group is optionally substituted with from 1 to 7 halogen substituents and/or with from 1 to 3 substituents each independently selected from hydroxy, cyano, C1-C4alkyl, C1-C4alkylthio (optionally substituted with from 1 to 3 halogen atoms) and C1-C4alkoxy (optionally substituted with from 1 to 3 halogen atoms); R2 is H, C1-C4alkyl (optionally substituted with from 1 to 7 halogen atoms), C₁-C₄alkyl-S(O)_x- wherein x is 0, 1 or 2 (optionally substituted with from 1 to 7 halogen atoms), C₁-C₄alkoxy (optionally substituted with from 1 to 7 halogen atoms), cyano, halogen, phenyl (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C_1 - C_4 alkyl and C_1 - C_4 alkoxy), phenoxy (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C_1 - C_4 alkyl and C_1 - C_4 alkoxy) or - CO_2 (C_1 - C_4 alkyl), or together with R3 forms a further benzene ring (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C₁-C₄alkyl and C₁-C₄alkoxy); R3 is H, C₁-C₄alkyl (optionally substituted with from 1 to 7 halogen atoms), C₁-C₄alkyl-S(O)_Xwherein x is 0, 1 or 2 (optionally substituted with from 1 to 7 halogen atoms), C₁-C4alkoxy (optionally substituted with from 1 to 7 halogen atoms), cyano, halogen, phenyl (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C1-C4alkyl and C1-C4alkoxy), phenoxy (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C1-C4alkyl and C1-C4alkoxy) or -CO2(C1-C4alkyl), or together with R2 or R4 forms a further benzene ring (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C₁-C₄alkyl and C₁-C₄alkoxy); R4 is H, C₁-C₄alkyl (optionally substituted

with from 1 to 7 halogen atoms), C_1 - C_4 alkyl- $S(O)_x$ - wherein x is 0, 1 or 2 (optionally substituted with from 1 to 7 halogen atoms), C₁-C₄alkoxy (optionally substituted with from 1 to 7 halogen atoms), cyano, halogen, phenyl (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C₁-C₄alkyl and C₁-C₄alkoxy), phenoxy (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C₁-C₄alkyl and C₁-C₄alkoxy) or -CO₂(C₁-C₄alkyl), or together with R3 forms a further benzene ring (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C₁-C₄alkyl and C₁-C₄alkoxy); R5 is H, C₁-C₄alkyl (optionally substituted with from 1 to 7 halogen atoms), C₁-C₄alkoxy (optionally substituted with from 1 to 7 halogen atoms) or halogen; R6 is H, C₁-C₄alkyl (optionally substituted with from 1 to 7 halogen atoms), C₁-C₄alkoxy (optionally substituted with from 1 to 7 halogen atoms) or halogen; R7 is H or C₁-C₄alkyl; R8 is H or C₁-C₄alkyl; R9 is H, halogen, hydroxy, cyano, C₁-C₄alkyl or C₁-C₄alkoxy; and R10 is H, halogen, hydroxy, cyano, C₁-C₄alkyl or C₁-C₄alkoxy; or a pharmaceutically acceptable salt thereof, with the proviso that the compound N-ethyl-N-benzyl-4piperidinamine is excluded;

a compound of formula (IB):

5

10

15

20

25

wherein Rx is H; Ry is H or C_1 - C_4 alkyl; each Rz is independently H or C_1 - C_4 alkyl; X represents O; Y represents OH or OR; R is C_1 - C_4 alkyl; Ar₁ is a phenyl ring or a 5- or 6-membered heteroaryl ring each of which may be substituted with 1, 2, 3, 4 or 5 substituents (depending upon the number of available substitution positions) each independently selected from C_1 - C_4 alkyl, $O(C_1$ - C_4 alkyl), $S(C_1$ - C_4 alkyl), halo, hydroxy, pyridyl, thiophenyl and phenyl optionally substituted with 1, 2, 3, 4 or 5 substituents each independently selected from halo, C_1 - C_4 alkyl, or $O(C_1$ - C_4 alkyl); and Ar_2 is a phenyl ring or a 5- or 6-membered

5

10

15

20

heteroaryl ring each of which may be substituted with 1, 2, 3, 4 or 5 substituents (depending upon the number of available substitution positions) each independently selected from C_1 - C_4 alkyl, $O(C_1$ - C_4 alkyl) and halo; wherein each above-mentioned C_1 - C_4 alkyl group is optionally substituted with one or more halo atoms; or a pharmaceutically acceptable salt thereof;

a compound of formula (IC)

$$\begin{array}{c|c}
R^1 & O & A \\
R^1 & O & X \\
R^1 & R & R^1
\end{array}$$
(IC)

wherein: A is S or O; R is H; Ar is a phenyl group optionally substituted with 1, 2, 3, 4 or 5 substituents each independently selected from C_1 - C_4 alkyl, $O(C_1$ - C_4 alkyl), $S(C_1$ - C_4 alkyl), halo, hydroxy, $CO_2(C_1$ - C_4 alkyl), pyridyl, thiophenyl and phenyl optionally substituted with 1, 2, 3, 4 or 5 substituents each independently selected from halo, C_1 - C_4 alkyl, or $O(C_1$ - C_4 alkyl); X is a phenyl group optionally substituted with 1, 2, 3, 4 or 5 substituents each independently selected from halo, C_1 - C_4 alkyl, or $O(C_1$ - C_4 alkyl); a C_1 - C_4 alkyl group; a C_3 - C_6 cycloalkyl group or a C_1 - C_4 alkyl; wherein each above-mentioned C_1 - C_4 alkyl group is optionally substituted with one or more halo atoms; or a pharmaceutically acceptable salt thereof; with the proviso that, when A is O, X is a C_1 - C_4 alkyl group, a C_3 - C_6 cycloalkyl group or a C_1 - C_4 cycloalkyl group;

a compound of formula (ID)

$$\begin{array}{c|c}
R^{3} & \downarrow & \downarrow & \downarrow \\
N & \downarrow & \downarrow & \downarrow \\
N & \downarrow & \downarrow & \downarrow \\
N & \downarrow & \downarrow & \downarrow \\
Ar & & \downarrow & \downarrow \\
O & & \downarrow & \downarrow \\
(ID)
\end{array}$$

-331-

wherein -X- is -C(R⁴R⁵)-, -O- or -S-; n is 2 or 3; R¹ is H or C_1 - C_4 alkyl; R³ is H, halo, C_1 - C_4 alkyl, O(C_1 - C_4 alkyl), nitrile, phenyl or substituted phenyl; R⁴ and R⁵ are each independently selected from H or C_1 - C_4 alkyl; Ar- is selected from the group consisting of

(i)
$$R^{2a}$$
 and (ii) R^{2e} R^{2d}

in which R^{2a} is H, halo, methyl or ethyl; R^{2b} is H, halo or methyl; R^{2c} is H, halo, methyl, trifluoromethyl, nitrile, or methoxy; R^{2d} is H, halo, methyl or ethyl; R^{2e} is H, halo, methyl, trifluoromethyl, nitrile, or methoxy; R^{2f} is H, or fluoro; -Y- is -O-, -S- or -N(R^6)-; and R^6 is H or methyl or a pharmaceutically acceptable salt thereof;

a compound of formula (IE)

5

10

15

20

wherein R^1 is C_1 - C_6 alkyl (optionally substituted with 1, 2 or 3 halo substituents and/or with 1 substituent selected from -S-(C_1 - C_3 alkyl), -O-(C_1 - C_3 alkyl) (optionally substituted with 1, 2 or 3 F atoms), -O-(C_3 - C_6 cycloalkyl), -SO₂-(C_1 - C_3 alkyl), -CN, -COO-(C_1 - C_2 alkyl) and -OH); C_2 - C_6 alkenyl; -(CH_2) $_0$ -Ar $_2$; or a group of formula (i) or (ii)

$$(CH_2)_{t}$$
 Z $(CR^5R^6)_{s}$ $(CH_2)_{t}$ $(CH_2)_{p}$ $(CR^7R^8)_{t}$ $($

 R^2 , R^3 and R^4 are each independently selected from hydrogen or C_1 - C_2 alkyl; R^5 , R^6 , R^7 and R^8 are at each occurrence independently selected from hydrogen or C_1 - C_2 alkyl; -X- is a bond, -CH₂-, -CH=CH-, -O-, -S-, or -SO₂-; -Y- is a bond, -CH₂- or -O-; -Z is hydrogen, -OH or -O-(C_1 - C_3 alkyl); p is 0, 1 or 2; q is 0, 1 or 2; r is 0 or 1; s is 0, 1, 2 or 3; t is 0, 1, 2 or 3; Ar₁ is phenyl, pyridyl, thiazolyl, benzothiophenyl or naphthyl; wherein said phenyl, pyridyl or

-332-

thiazolyl group may be substituted with 1, 2 or 3 substituents each independently selected from halo, cyano, C₁-C₄ alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C₁-C₄ alkyl) (optionally substituted with 1, 2 or 3 F atoms) and -S-(C₁-C₄ alkyl) (optionally substituted with 1, 2 or 3 F atoms) and/or with 1 substituent selected from pyridyl, pyrazole, phenyl (optionally substituted with 1, 2 or 3 halo substituents) and phenoxy (optionally substituted with 1, 2 or 3 halo substituents); and wherein said benzothiophenyl or naphthyl group may be optionally substituted with 1, 2 or 3 substituents each independently selected from halo, cyano, C₁-C₄ alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C₁-C₄ alkyl) (optionally substituted with 1, 2 or 3 F atoms), and -S-(C₁-C₄ alkyl) (optionally substituted with 1, 2 or 3 F atoms); Ar₂ is naphthyl, pyridyl, thiazolyl, furyl, thiophenyl, benzothiophenyl, or phenyl, wherein said naphthyl, pyridyl, thiazolyl, furyl, thiophenyl, benzothiophenyl, or phenyl may be substituted with 1, 2 or 3 substituents each independently selected from halo, C1-C4 alkyl (optionally substituted with 1, 2 or 3 F atoms) and -O-(C1-C4 alkyl) (optionally substituted with 1, 2 or 3 F atoms); or a pharmaceutically acceptable salt thereof; provided that (a) the cyclic portion of the group of formula (i) must contain at least three carbon atoms and not more than seven ring atoms; (b) when -X- is -CH=CH-, then the cyclic portion of the group of formula (i) must contain at least five carbon atoms; and (c) when -Z is -OH or -O-(C₁-C₃ alkyl), then -X- is -CH₂-; (d) when -Y- is -O- then p cannot be 0; and (e) the compound 3-[(phenylmethyl)-(3S)-3-pyrrolidinylamino]-propanenitrile is excluded;

a compound of formula (IF)

$$\begin{array}{c|c}
R^2 & 1 \\
N & Ar_1 \\
R^3 & R^4
\end{array}$$
(IF)

25 wherein

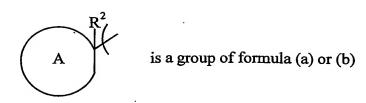
5

10

15

20

-333-



$$\begin{array}{cccc}
& & & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
& & & \\
&$$

 R^1 is C_1 - C_6 alkyl (optionally substituted with 1, 2 or 3 halo substituents and/or with 1 substituent selected from -S-(C_1 - C_3 alkyl), -O-(C_1 - C_3 alkyl) (optionally substituted with 1, 2 or 3 F atoms), -O-(C_3 - C_6 cycloalkyl), -SO₂-(C_1 - C_3 alkyl), -CN, -COO-(C_1 - C_2 alkyl) and -OH); C_2 - C_6 alkenyl; -(C_1 - C_2 - C_3 - C_6 alkenyl; -(C_1 - C_2 - C_6 - C_1 - C_2 - C_3 - C_6 - C_1 - C_2 - C_3 - C_4 - C_5 - C_6 - C_5 - C_6 - C_7 - C_8 -C

5

10

15

20

$$(CH_2)_{t}$$
 Z $(CR^5R^6)_{s}$ $(CH_2)_{r}$ (CR^5R^6) $(CH_2)_{p}$ $(CR^7R^8)_{t}$ $(CR^7$

 R^2 , R^3 and R^4 are each independently selected from hydrogen or C_1 - C_2 alkyl; R^5 , R^6 , R^7 and R^8 are at each occurrence independently selected from hydrogen or C_1 - C_2 alkyl; -X- is a bond, -CH₂-, -CH=CH-, -O-, -S-, or -SO₂-; -Y- is a bond, -CH₂- or -O-; -Z is hydrogen, -OH or -O-(C_1 - C_3 alkyl); p is 0, 1 or 2; q is 0, 1 or 2; r is 0 or 1; s is 0, 1, 2 or 3; t is 0, 1, 2 or 3; Ar₁ is phenyl, pyridyl, thiazolyl, benzothiophenyl or naphthyl; wherein said phenyl, pyridyl or thiazolyl group may be substituted with 1, 2 or 3 substituents each independently selected from halo, cyano, C_1 - C_4 alkyl (optionally substituted with 1, 2 or 3 F atoms) and -S-(C_1 - C_4 alkyl) (optionally substituted with 1, 2 or 3 F atoms) and -S-(C_1 - C_4 alkyl) (optionally substituted with 1, 2 or 3 halo substituents), benzyl and phenoxy (optionally substituted with 1, 2 or 3 halo substituents); and wherein said benzothiophenyl or naphthyl group may be optionally substituted with 1, 2 or 3 substituted with 1, 2 or 3 F atoms), -O-(C_1 - C_4 alkyl (optionally substituted with 1, 2 or 3 substituted with 1, 2 or 3 F atoms), -O-(C_1 - C_4 alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C_1 - C_4 alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C_1 - C_4 alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C_1 - C_4 alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C_1 - C_4 alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C_1 - C_4 alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C_1 - C_4 alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C_1 - C_4 alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C_1 - C_4 alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C_1 - C_4 alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C_1 - C_4 alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C_1 - C_4 alkyl (optionally substituted with 1, 2 or 3 F atoms)

 C_4 alkyl) (optionally substituted with 1, 2 or 3 F atoms), and -S-(C_1 - C_4 alkyl) (optionally substituted with 1, 2 or 3 F atoms); Ar₂ is naphthyl, pyridyl, thiazolyl, furyl, thiophenyl, benzothiophenyl, or phenyl may be substituted with 1, 2 or 3 substituents each independently selected from halo, C_1 - C_4 alkyl (optionally substituted with 1, 2 or 3 F atoms) and -O-(C_1 - C_4 alkyl) (optionally substituted with 1, 2 or 3 F atoms); or a pharmaceutically acceptable salt thereof; provided that (a) the cyclic portion of the group of formula (i) must contain at least three carbon atoms and not more than seven ring atoms; (b) when -X- is -CH=CH-, then the cyclic portion of the group of formula (i) must contain at least five carbon atoms; and (c) when -Z is -OH or -O-(C_1 - C_3 alkyl), then -X- is -CH₂-; and (d) when -Y- is -O- then p cannot be 0;

a compound of formula (IG)

5

10

15

20

wherein -X- is -S- or -O-; each R is independently selected from H or C_1 - C_4 alkyl; R^1 is H, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, halo, cyano, trifluoromethyl, trifluoromethoxy, -NR³R⁴, -CONR³R⁴, -COOR³ or a group of the formula (i)

$$-z$$
 R^5

R² is C₁-C₄ alkyl, phenyl or phenyl substituted with 1, 2 or 3 substituents each independently selected from C₁-C₄ alkyl, C₁-C₄ alkoxy, nitro, hydroxy, cyano, halo, trifluoromethyl, trifluoromethoxy, benzyl, benzyloxy, -NR⁶R⁷, -CONR⁶R⁷, COOR⁶, -SO₂NR⁶R⁷ and -SO₂R⁶; R⁵ is selected from C₁-C₄ alkyl, C₁-C₄ alkoxy, carboxy, nitro, hydroxy, cyano, halo, trifluoromethyl, trifluoromethoxy, benzyl, benzyloxy, -NR⁸R⁹, -CONR⁸R⁹, -SO₂NR⁸R⁹ and -

-335-

SO₂R⁸; R³, R⁴, R⁶, R⁷, R⁸ and R⁹ are each independently selected from H or C₁- C₄ alkyl; and -Z- is a bond, -CH₂-, or -O-; or a pharmaceutically acceptable salt thereof and a compound of formula (IH)

5

15

20

25

wherein,

X is OH, C1-C4 alkoxy, NH₂ or NH(C1-C4 alkyl);

Rx is H or C1-C4 alkyl;

Ry is H or C1-C4 alkyl;

each Rz group is independently H or C1-C4 alkyl, with the proviso that not more than 3 Rz groups may be C1-C4 alkyl;

R1 is C1-C6 alkyl (optionally substituted with 1, 2 or 3 halogen atoms and/or with 1 substituent selected from C1-C4 alkylthio (optionally substituted with 1, 2 or 3 fluorine atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 fluorine atoms), C3-C6 cycloalkoxy, C1-C4 alkylsulfonyl, cyano, -CO-O(C1-C2 alkyl), -O-CO-(C1-C2 alkyl) and hydroxy); C2-C6 alkenyl (optionally substituted with 1, 2 or 3 halogen atoms); C3-C6 cycloalkyl (optionally substituted with 1, 2 or 3 halogen atoms and/or with 1 substituent selected from C1-C4 alkoxy and hydroxy) wherein one C-C bond within the cycloalkyl moiety is optionally substituted by an O-C, S-C or C=C bond; C4-C7 cycloalkylalkyl (optionally substituted with 1, 2 or 3 halogen atoms and/or with 1 substituent selected from C1-C4 alkoxy and hydroxy) wherein one C-C bond within the cycloalkyl moiety is optionally substituted by an O-C, S-C or C=C bond; or CH₂Ar₂; and Arl and Ar2 are each independently a phenyl ring or a 5- or 6-membered heteroaryl ring each of which is optionally substituted with 1, 2 or 3 substituents (depending upon the number of available substitution positions) each independently selected from C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkylthio (optionally substituted with 1, 2 or 3 halogen atoms), -CO-O(C1-C4 alkyl), cyano, -NRR, -CONRR, halo and hydroxy

-336-

and/or with 1 substituent selected from pyridyl, thiophenyl, phenyl, benzyl and phenoxy each of which is optionally ring-substituted with 1, 2 or 3 substituents each independently selected from halogen, C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), carboxy, nitro, hydroxy, cyano, -NRR, -CONRR, SO₂NRR and SO₂R); and each R is independently H or C1-C4 alkyl;

or a pharmaceutically acceptable salt thereof.

5

10

3. The method of claim 1 or the use of claim 2, wherein said selective norepinephrine reuptake inhibitor is atomoxetine hydrochloride.